CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74787

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74787 SPONSOR: Zenith Goldline Pharm. Inc.
DRUG & DOSAGE FORM : Labetalol Hydrochloride Tablet
STRENGTH (s) : 100, 200 and 300 mg
TYPE OF STUDY: SD XXX SDF XXX OTHER Dissolution
STUDY SITE: CLINICAL:
ANALYTICAL:

STUDY SUMMARY :

The firm has conducted bio-studies on the middle i.e. 200 mg strength against the 'Orange Book' recommended 300 mg. The firm claims to have done this due to the perceived safety concern of administering the 300 mg dose to healthy volunteers which was expressed by the contract research labs's medical officer at that time. Studies on the 200 mg strength are acceptable. Based on the formulation proportionality and comparable dissolution, a bio-study waiver of 100 mg strength is granted. A one time bio-study waiver for 300 mg strength is granted based on the premise that the firm did follow the opinion of the medical officer at that time, based on the subject safety.

DISSOLUTION :Acceptable.

PRIMARY REVIEWER :Pradeep M. Sathe, Ph.D. BRANCH : I

INITIAL : /S/ DATE : 4/29/98

Team Leader : Yih Chain Huang, Ph.D. BRANCH : I

INITIAL : YCH DATE : 4/29/98

DIRECTOR : Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 4/30/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

2.1

Labetalol Hydrochloride
100 mg, 200 mg, 300 mg tablet
ANDA 74-787
Reviewer: Pradeep M. Sathe, Ph.D.
WP # 74787O.997

Zenith Goldline Pharm. Inc.
Northvale, NJ-07647
Submission Date:
September 26, 1997

REVIEW OF AN AMENDMENT

I.INTRODUCTION : Labetalol is an adrenergic receptor blocking agent that has both selective α_1- and non-selective β-adrenergic receptor blocking actions. Labetalol HCl is a racemate, chemically designated as 5-[1-hydroxy-2[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride.It has the empirical formula $C_{19}H_{24}N_2O_3$.HCl corresponding to a molecular weight of 364.9. The chemical structure shows two asymmetric centers. The drug therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R' stereoisomer, makes up 25% of racemic labetalol. Commercially, labetalol HCl is available as a white to off-white crystalline powder, soluble in water.

Labetalol pharmacokinetics is characterized by a high first pass, the oral availability being around 18%. Approximately 50% of the drug is bound to the plasma proteins. The clearance is around 25 ml/min/kg. Less than 5% of the drug is excreted in urine. Volume of distribution is about 9.4 liters/kg and half-life is around 4.9 hr.

II.CURRENT SUBMISSION : The current application is an amendment to the application dated November 14, 1995. The compositions for the 100 mg, 200 mg and 300 mg strength formulations are given in Table 'A'. The 100 mg, 200 mg and 300 mg formulations have a film coat, corresponding to a theoretical weight gain of 4 mg, 8 mg and 12 mg respectively for the 100 mg, 200 mg and 300 mg strengths. The corresponding film coating specifications for the actual weight gains are (2-6 mg) for 4 mg theoretical gain, (6-10 mg) for the 8 mg theoretical gain and (10-14 mg) for the 12 mg theoretical gain. When analyzed, it was noticed that the actual weight gain of the 200 mg strength bio-batch (ND-241), was 4.7 mg which was slightly less than the set specifications (6-10 mg). The firm therefore manufactured another batch which showed an actual weight gain of 9.8 mg, complying with the specifications of 6-10 mg. In support of the increase in the film coat weight, the firm has provided the dissolution data on the newly manufactured batch (ND-398). The dissolution data corresponding to the bio-equivalence study batch (ND-241) and the newly manufactured batch (ND-398) are given in Table I.

III.TEST FORMULATION : Table 'A' gives the composition of the test formulations.

Table 'A'

	100 mg		200 mg		300 mg	
Component	mg/tab	w/w%	mg/tab	w/w%	mg/tab	w/w%
Core						
Labetalol HCl USP						
Lactose Monohydrate						
Starch, NF						
Sodium Starch Glycolate, NF						
Hydroxypropyl Methyl Cellulose						
Magnesium Stearate						
Purified Water						
Film Coating(specs)						
Opadry Yellow						
Opadry White						
Opadry Green						
Purified Water						
Total Average Tablet Weight						

Labetalol, the active ingredient, is also proportionally highest. Lactose, Starch and Sodium starch glycolate are the excipients. Hydroxypropyl methyl cellulose is a pharmaceutical aid and magnesium stearate is the lubricant. The 100 mg, 200 mg, and 300 mg test formulations are proportional with respect to mg/tablet content and are adjusted to an identical weight percentage for all the ingredients across the strengths.

IV.DISSOLUTION METHODOLOGY : The firm has used the following USP XXIII recommended dissolution testing methodology and specifications for the comparative dissolutions of the test and reference formulations.

Apparatus: USP XXIII, 2 (paddle)
Speed: 50 rpm
Medium: Deaerated Water
Volume: 900 ml

A. RESULTS OF THE DISSOLUTION TESTING : The comparative dissolutions for the 200 mg bio-lot and the newly manufactured lot formulations are given in Table I.

B. COMMENTS ABOUT THE DISSOLUTION TESTING :

1. The dissolution testing indicates that both batches pass the USP recommended 'Q' comfortably and there is no adverse impact on the drug release due to increased weight of film coating.

V.RECOMMENDATIONS :

1. The bioequivalence study conducted by Zenith-Goldline Labs on its 200 mg labetalol hydrochloride tablet, lot # ND-241, comparing it to Schering's Normodyne^{R} 200 mg tablet, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Zenith-Goldline Labs, labetalol hydrochloride 200 mg tablet is bioequivalent to the reference product Normodyne^{R} 200 mg tablet manufactured by Schering Labs.

2. The dissolution testing data conducted by Zenith-Goldline Labs on its Labetalol hydrochloride 200 mg tablet, lot #ND-241, and ND-398 respectively are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of deaerated water at 37^{0}C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in minutes.

/S/

(1) 4/29/98

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 4/27/98

Concur: Date: 4/28/98

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-787 (Original, Duplicate), HFD-650 (Director), HFD-652 (Sathe), Drug File, Division File.

Table I . In-Vitro Dissolution Testing

Drug (Generic Name): Labetalol Hydrochloride
Dose Strength: 100 mg, 200 mg and 300 mg tablet
ANDA No.: 74-787
Firm: Zenith-Goldline Labs.
Submission Date: September 26, 1997
File Name: 74787O.997

I. Conditions for Dissolution Testing:

USP XXIII Method 2, Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water, Volume: 900 ml
Specifications: NLT % (Q) dissolved in minutes
Reference Listed Drug Product: Normodyne[R] Tablet
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Reference Product : Zenith's Labetalol HCl tablet Lot # ND-241 Strength (200 mg)			Test Product : Zenith's Labetalol HCl tablet Lot # ND-398 Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	90.9		4.7	90.1		3.8
20	92.7		3.3	92.9		2.3
30	93.7		2.7	93.7		1.8
45	94.1		2.1	94.2		1.5
60	94.3		2.0	94.9		1.3

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 74-787 APPLICANT:Zenith Goldline Pharm. Inc.

DRUG PRODUCT:Labetalol Hydrochloride, 100 mg, 200 mg, 300 mg tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in the earlier communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 20 1996

Labetalol Hydrochloride
100 mg, 200 mg, 300 mg tablet
ANDA 74-787
Reviewer: Pradeep M. Sathe, Ph.D.
WP # 74787SDW.N95

Zenith Goldline Pharm. Inc.
Northvale, NJ-07647
Submission Date:
November 14, 1995

REVIEW OF TWO BIO-STUDIES, DISSOLUTION AND WAIVER REQUESTS

I.INTRODUCTION : Labetalol is an adrenergic receptor blocking agent that has both selective α_1- and non-selective β-adrenergic receptor blocking actions. Labetalol HCl is a racemate, chemically designated as 5-[1-hydroxy-2[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride. It has the empirical formula $C_{19}H_{24}N_2O_3.HCl$ corresponding to a molecular weight of 364.9. The chemical structure shows two asymmetric centers. The drug therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R' stereoisomer, makes up 25% of racemic labetalol. Commercially, labetalol HCl is available as a white to off-white crystalline powder, soluble in water.

Labetalol pharmacokinetics is characterized by a high first pass, the oral availability being around 18%. Approximately 50% of the drug is bound to the plasma proteins. The clearance is around 25 ml/min/kg. Less than 5% of the drug is excreted by urine. Volume of distribution is about 9.4 liters/kg and half-life is around 4.9 hr.

II.CURRENT SUBMISSION : The application consists of A] a single dose fasting bio-equivalency study comparing 200 mg test (Zenith Goldline) and 200 mg reference (Schering's Normodyne^R) tablet formulations, B] a single dose "food challenge" bio-equivalency study comparing 200 mg test (Zenith Goldline) and 200 mg reference (Schering's Normodyne^R) labetalol hydrochloride tablet formulations, C] dissolution testing methodology and data comparing the test and the reference formulations of the 100 mg, 200 mg and 300 mg strengths and D] bio-equivalence study waiver requests for the test formulations of 100 mg and 300 mg strengths.

At present, there are two labetalol tablet formulations on the market. One is Schering's Normodyne^R, which is also a reference formulation and the other is Glaxo's 'Trandate'. Since both of these formulations were filed as NDA's, the current formulation, if approved, will be the first generic. The labelling does not advice the drug to be administered specifically in relation to the food intake, however it is recommended to be administered in a twice a day dosing regimen with individualized dosing. The recommended dose ranges from 100 mg initial dose to up to 400 mg maintenance dose.

III.TEST FORMULATION : Table 'A' gives the composition of the test formulations.

Table 'A'

	100 mg		200 mg		300 mg	
Component	mg/tab	w/w%	mg/tab	w/w%	mg/tab	w/w%
Core						
Labetalol HCl USP						
Lactose Monohydrate						
Starch, NF						
Sodium Starch Glycolate, NF						
Hydroxypropyl Methyl Cellulose						
Magnesium Stearate						
Purified Water						
Film Coating						
Opadry Yellow						
Opadry White						
Opadry Green						
Purified Water						
Total Average Tablet Weight						

Labetalol, the active ingredient, is also proportionally highest. Lactose, Starch and Sodium starch glycolate are the excipients. Hydroxypropyl methyl cellulose is a pharmaceutical aid and magnesium stearate is the lubricant. The 100 mg, 200 mg, and 300 mg test formulations are proportional with respect to mg/tablet content and are adjusted to an identical weight percentage for all the ingredients across the strengths.

IV.BIO-STUDY NO. 037-67-10756, FASTING BIOEQUIVALENCY STUDY :

A. TITLE : Bioavailability of Labetalol HCl tablets, 200 mg.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Principal Investigator :

2. Bio-Study Site :

3. Project Director :

4. Analytical Investigator :

5. Study Periods : Phase I, Group 1 : September 30 to October 3, 1994
Phase II, Group 1 : October 7 to October 10, 1994

Phase I, Group 2 : October 8 to October 11, 1994
Phase II, Group 2 : October 15 to October 18, 1994

C. STUDY OBJECTIVE : To compare the plasma levels of Labetalol produced after administration of the test formulation with those produced after administration of a marketed reference product, under fasting conditions.

D. STUDY DESIGN AND NUMBER OF SUBJECTS : This was a randomized two-way crossover design involving 37 subjects. There was a seven day washout period between the two study phases. Forty (40) subjects were entered in the study. Thirty-seven (37) completed the study. Three subjects could not complete the study for the following reasons: Subject #12 tested positive for cocaine prior to Phase II dosing and was withdrawn from the study. Subject #25 voluntarily withdrew from the study and left the facility against medical advice at 8:00 p.m. on 10/09/94, in Phase I. Subject #28 tested positive for alcohol prior to phase II and was withdrawn from the study.

E. SUBJECT SELECTION CRITERIA : Volunteers were selected in the study if they met the following:

1. Male, healthy, 18-50 years of age.

2. No more than ± 15% from ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.
3. Without a history of asthma, diabetes, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases, alcohol or drug abuse as evidenced by a medical history and physical examination obtained within 30 days prior to the start of the study. Deviations were be acceptable if deemed not clinically significant by the investigator.
4. Blood chemistry (alkaline phosphatase, glucose, SGOT, SGPT, LDH, BUN, GGT, creatinine, bilirubin, electrolytes), hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count), and urinalysis values within clinically acceptable limits upon evaluation by the investigator. The tests were performed within 30 days prior to the start of the study.
5. No prescription drugs within 14 days or OTC medications (excluding acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration.
6. No alcohol consumption for at least 24 hours prior to the drug administration, in each phase.
7. No known allergy to labetalol, or other alpha or beta blockers.
8. Subjects had a minimum screening and/or check-in blood pressure of 100/70 mm Hg.
9. Acceptable ECG: sinus rhythm with no evidence of first degree AV block.
10. No caffeine for at least 12 hours prior to dosing in each phase.
11. Negative HIV-1, hepatitis-B surface antigen and urine screen for drugs of abuse within 30 days prior to the start of the study. Negative urine screen for drugs of abuse at check-in, both phases.

F. SUBJECT RESTRICTIONS : The following restrictions appear to have been placed on the subjects throughout the study:

1. The subjects were housed in the PharmaKinetics live-in facility from at least 12 hours before until at least 24 hours after drug administration.
2. The subjects were not allowed to smoke from 1 hour prior until 4 hours after drug administration or within 1 hour prior to scheduled blood pressure measurements.
3. Subjects were required to be supine for 6 hours after the dose. No strenuous physical activity was permitted during the in-house portion of the study.
4. Subjects fasted for at least 10 hours prior to and 5 hours after the drug administration.
5. No alcohol, xanthine-containing beverages or concurrent medications were allowed.

G. STUDY SCHEDULES :

1. **Methods** : The study was planned to be carried out in two groups of 20 subjects

(total 40 subjects). On the study day, based on the randomization scheme, the subjects were administered 200 mg of either the test or the reference formulation with 240 ml water. The subjects were asked to remain supine for 6 hours post-dose. A standardized lunch and dinner were served at 6 hr and 10 hr following the dose. Only xanthine-free foods and beverages were provided. Blood samples were drawn at regular intervals as per the sample scheme. Blood pressure and pulse were monitored at regular intervals.

2. **Randomization Schedule** : The randomization schedule is given for the two groups, each comprising 20 subjects.

Treatment

Group I

Phase I	Phase II	Volunteer Number
A	B	2, 3, 6, 8, 9, 11, 14, 16, 18, 19
B	A	1, 4, 5, 7, 10, 12, 13, 15, 17, 20

Group II

Phase I	Phase II	Volunteer Number
A	B	22, 23, 26, 27, 29, 31, 34, 35, 37, 40
B	A	21, 24, 25, 28, 30, 32, 33, 36, 38, 39

3. **Blood Sampling** : Ten (10) ml of venous blood was drawn in Vacutainers^{R} containing EDTA anticoagulant at: 0 (pre-dose), 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 10.0, 14.0, 18.0, 24.0, 30.0, 36.0 and 48.0 hours post-dose. The samples were then centrifuged at 10^{0}C and 2500 rpm for approximately 20 minutes. The plasma samples were separated and stored at -20^{0}C.

4. Safety Monitoring: Blood pressure and pulse were obtained supine and standing at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0 hours post-dose. Seated blood pressure and pulse were monitored prior to drug administration and at 6, 12 and 24 hours following dosing.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Labetalol HCl tablet, 200 mg (Zenith Labs.), Lot #ND-241, Assay Potency=99.5%, Batch Size:

2. REFERENCE PRODUCT B : Normodyne^{R} (Labetalol HCl) tablet, 200 mg (Schering), Lot #94063, Assay Potency=100.3%, Expiry date: 8/96

I. ASSAY METHODOLOGY : **The following assay methodology may be a proprietary information of the firm and therefore should not be released under F.O.I.**

J. PHARMACOKINETICS AND STATISTICS : The following pharmacokinetic parameters were evaluated: area under the curve until the last sample point, AUC(0-t), area under the curve until the infinite time, AUC(0-inf), maximum observed concentration, Cmax, time of the maximum concentration, Tmax and half-life $T_{1/2}$. The untransformed and log-transformed parameters were evaluated using analysis of variance. Since the dosing was done in two groups, the statistics used the following factors in the ANOVA model: group, sequence, group*sequence, subject(group*sequence), period(group), treatment and group*treatment. The two one-sided test procedure was used for the assessment of bioequivalence.

K. RESULTS OF THE BIOEQUIVALENCY STUDY :
The mean labetalol plasma concentration time data is as given in table BST 1.1. The mean plasma level time profile graph is given in Attachment BSF 1.1.

Table BST 1.1 : Mean (arithmetic) labetalol levels (ng/ml) of the test and reference formulations. Standard Deviations are given in the parentheses.

Time (hr)	Test (Zenith)	Reference (Schering)	Test/Ref. Ratio
0.0	0.0 (---)	0.0 (---)	-----
0.25	43.76 (51.05)	31.21 (57.75)	1.40
0.5	103.4 (70.63)	99.26 (74.82)	1.04
1.0	91.71 (34.16)	100.6 (41.71)	0.91
1.5	62.68 (22.82)	73.30 (30.34)	0.86
2.0	55.80 (28.60)	56.81 (22.96)	0.98
2.5	42.57 (17.91)	42.95 (15.98)	0.99
3.0	36.29 (15.73)	37.19 (15.40)	0.98
4.0	28.38 (12.27)	29.96 (12.19)	0.95
6.0	23.07 (10.33)	22.90 (9.334)	1.01
10.0	14.06 (6.126)	14.32 (6.571)	0.98
14.0	7.375 (4.991)	8.051 (4.198)	0.92
18.0	4.519 (4.532)	4.708 (4.400)	0.96
24.0	1.827 (3.379)	1.754 (3.618)	1.04
30.0	0.7978 (2.434)	0.3162 (1.923)	2.52
36.0	0.1770 (1.077)	0.2584 (1.572)	0.68
48.0	0.000 (0.000)	0.1392 (0.847)	0.00

The mean pharmacokinetic parameters and statistics are given in table BST 1.2. The parameters are expressed in the following units: AUC as ng/ml*hr, Cmax as ng/ml, Tmax and $T_{1/2}$ as hr. The parameters were evaluated by considering the arithmetic, geometric and LSMEANS.

Table BST 1.2 : Mean labetalol Pharmacokinetic Parameters, fasting study. Numbers in parentheses represent standard deviations for the arithmetic means and standard errors for the LSMEANS

PK parameter	Test (Zenith)	Reference (Schering)	Ratio (T/R)	90% Confidence Interval
AUC(0-t)	423.9 (189.3)	435.5 (203.8)	0.97	
LnAUC(0-t), Geom.Mean	5.97 (0.40), 391.5	6.00 (0.36), 404.7	0.97	
AUC(0-inf)	477.4 (198)	497.6 (214.1)	0.96	
LnAUC(0-inf), Geom.Mean	6.10 (0.36), 446.8	6.15 (0.34), 467.5	0.96	
Cmax	137.5 (48.3)	136.3 (51.7)	1.01	
LnCmax, Geom.Mean	4.85 (0.40), 128.2	4.85 (0.37), 127.5	1.01	
Tmax	0.80 (0.44)	0.92 (0.46)	0.87	
$T_{1/2}$	6.57 (2.6)	6.76 (2.4)	0.97	
AUC(0-t)*	421.4 (7.3)	433.5 (7.3)	0.97	0.93-1.01
LnAUC(0-t)*, Antilog	5.96 (0.02), 388.7	6.00 (0.02), 403.4	0.96	0.92-1.01
AUC(0-inf)*	478.2 (7.76)	495.8 (7.52)	0.96	0.93-1.00
LnAUC(0-inf)*, Antilog	6.10 (0.02) 445.9	6.14 (0.02) 464.1	0.96	0.92-1.00
Cmax*	137.8 (6.01)	136.1 (6.01)	1.01	0.91-1.12
LnCmax*, Antilog	4.85 (0.04), 128.0	4.85 (0.04), 127.5	1.00	0.90-1.12

* = LSMEANS

L. ADVERSE EFFECTS : The firm has reported adverse effects for all subjects. The adverse effects were of mild or moderate severity and included symptoms such as

headache, decreased diastolic blood pressure, tachycardia, itchy scalp, tiredness, congested nose, lightheadedness, blurred vision etc. Decreased diastolic blood pressure was the most commonly observed side effect with a possible to probable relationship with the drug. The side effects occurred with almost similar frequency for both formulations. The detailed adverse effects are reported in Attachment 1.

M. COMMENTS ON THE FASTING BIOEQUIVALENCY STUDY :

1. The mean plasma levels and the corresponding standard deviations are comparable for both treatments. Based on the detection limit of 5 ng/ml, it may be concluded that the elimination is over in about 24 hours.
2. The mean pharmacokinetic parameters for the two formulations are comparable and the 90% confidence intervals are within the range of % after log conversion implying the bioequivalence of the two treatments. The test/reference ratios are close to 1.0. The mean AUC(0-t)'s are more than 87% of the AUC(0-inf) indicating adequate sample duration.
3. It is not clear why the Kel could not be adequately calculated for subject #1 for the test formulation. When the analysis was conducted by including subject #1 Kel, it did not change the outcome of the bioequivalence conclusion.

V. BIO-STUDY NO. 037-73-10827, POST PRANDIAL STUDY

A. TITLE : Bioavailability of labetalol HCl tablets, 200 mg -effect of food study

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Principal Investigator, Bio-Study Site and Analytical Investigator : Same as for the previous study.

2. Clinical Study Dates :

Period I : Jan. 25-27, 1995
Period II : Feb. 1-3, 1995
Period III : Feb. 8-10, 1995.

C. STUDY OBJECTIVES :

1. To compare labetalol plasma levels produced after the test formulation is administered following a standard meal with those produced after a marketed reference product is administered following a standard meal.

2. To compare labetalol plasma levels produced after the test formulation is administered following a standard meal with those produced after administration of test formulation following an overnight fast.

D. STUDY DESIGN : This was a single dose three way crossover design, with a one week washout period between any two phases. A total of eighteen (18) subjects were enrolled in the study. Five subjects dropped out of the study and a total of thirteen (13) subjects completed the study. Subject #2 tested positive for alcohol prior to period III dosing and was withdrawn from the study. Subject #4 and #8 voluntarily withdrew from the study for personal reasons. Subject #9 was withdrawn from the study during period I after experiencing chest pain. The subject was transported to the hospital for evaluation. Subject #16 failed to return to the facility after completing period I.

E. SUBJECT SELECTION CRITERIA : Volunteer selection criteria was similar to the fasting study.

F. SUBJECT RESTRICTIONS : The restrictions were similar to the fasting study.

G. STUDY SCHEDULES :

1. **Methods** : The subjects were housed from approximately 12 hours prior to drug administration until 24 hours post-dose each period. On the study day, each subject was administered either treatment A, B or C depending on the randomization scheme with 240 ml water. Subjects receiving treatments A and B were served a standard breakfast 35 minutes prior to dosing. The breakfast consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash-brown potatoes, six fluid oz. (180 ml) of orange juice and eight fluid oz (240 ml) of whole milk. The subjects remained supine for six hours following drug administration. The subjects were not allowed to smoke 1 hour prior to dosing until 4 hours following drug administration.

2. **Randomization Schedule** : The following randomization schedule was used for 14 subjects:

Treatments			
Phase I	Phase II	Phase III	Volunteer Number
A	B	C	12, 14
B	C	A	2, 17
C	A	B	3, 11, 15

A	C	B	1, 7, 18
C	B	A	5, 10
B	A	C	6, 13

For the remaining 4 subjects, #4, #8, #9 and #16, the randomization is not reported and could not be figured out since they dropped out after the first period.

3. **Blood Sampling** : Ten (10) ml of venous blood was drawn in Vacutainers^{R} containing EDTA anticoagulant at: 0 (pre-dose), 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 10.0, 14.0, 18.0, and 24.0 hours post-dose. The samples were then centrifuged at 10^{0}C and 2500 rpm for approximately 20 minutes. The plasma samples were separated and stored at -20^{0}C. It is noted that compared to the fasting study, the firm has slightly modified the sampling scheme by not collecting the 30 hr, 36 hr and 48 hr samples as compared to the fasting study.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Labetalol HCl tablet, 200 mg (Zenith Labs.), Lot #ND-241, Assay Potency=99.5%, Batch Size , , with food

2. REFERENCE PRODUCT B : Normodyne^{R} tablet, 200 mg (Schering), Lot #94063, Assay Potency=100.3%, Expiry date: 8/96, with food

3. REFERENCE PRODUCT C : Labetalol HCl tablet, 200 mg (Zenith Labs.), Lot #ND-241, Assay Potency=99.5%, Batch Size: fasting

I. ASSAY METHODOLOGY : Similar to the fasting study.

J. PHARMACOKINETICS AND STATISTICS : Similar to the fasting study.

K. RESULTS OF THE POST PRANDIAL BIO-STUDY : The plasma concentration-time data for the three treatments along with their standard deviations are given in table BST 2.1. The mean pharmacokinetic parameters are listed in table BST 2.2. The mean plasma level profiles are given in Attachment BSF 2.1.

Table BST 2.1 : Mean (n=13) labetalol plasma concentrations with standard deviations in the parentheses.

Time (hr)	Trt. 'A' (Zenith, fed)	Trt. 'B' (Schering, fed)	Trt. 'C' (Zenith, fasting)	Ratio, A/B
0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	------
0.25	15.32 (52)	1.33 (4.6)	82.86 (89.5)	11.5
0.5	21.25 (32.8)	24.03 (38.9)	168.9 (135.6)	0.88
1	46.96 (46.5)	95.88 (85.7)	106.4 (63.3)	0.49
1.5	64.03 (36.3)	103.1 (77.5)	74.79 (42.1)	0.62
2	81.04 (36.5)	88.68 (59.2)	59.51 (40)	0.91
2.5	84.77 (42.8)	81.48 (49.1)	49.01 (32.3)	1.04
3	74.05 (43.6)	71.72 (42.6)	45.28 (32)	1.03
4	54.39 (35.5)	52.58 (31.7)	37.39 (26.6)	1.03
6	34.52 (21.4)	36.4 (23.1)	30.21 (21.5)	0.95
10	22.04 (15.2)	22.69 (16.2)	19.07 (13.5)	0.97
14	13.6 (10.2)	14.27 (12.8)	11.78 (10)	0.95
18	9.56 (8.0)	10.14 (9.3)	8.00 (8.5)	0.94
24	4.5 (7.3)	5.6 (8.0)	4.7 (7.3)	0.80

Table BST 2.2 : Mean labetalol Pharmacokinetic Parameters, Non-fasting study. Numbers in parentheses represent standard deviations for the arithmetic means and standard errors for the LSMEANS

PK parameter	Treatment A (Zenith, fed)	Treatment B (Schering, fed)	Treatment C (Zenith, fasting)	Ratio of A/B
AUC(0-t)	582.6 (368.3)	640.8 (459.9)	577.3 (438.4)	0.91
LnAUC(0-t), Geom.Mean	6.21 (0.56) 497.8	6.26 (0.65) 523.2	6.13 (0.70) 457.7	0.95
AUC(0-inf)	673.7 (433.5)	739.3 (541.7)	674.3 (511.5)	0.91
LnAUC(0-inf), Geom.Mean	6.35 (0.56) 574.4	6.40 (0.64) 602.3	6.30 (0.64) 544.8	0.95
Cmax	108.1 (44.9)	129.0 (71.9)	178.1 (131.1)	0.84
LnCmax, Geom.Mean	4.62 (0.37) 101.0	4.74 (0.51) 113.9	4.97 (0.67) 143.6	0.89
Tmax	1.98 (0.8)	1.54 (0.6)	0.67 (0.3)	1.28
$T_{1/2}$	6.5 (1.6)	6.5 (1.9)	7.5 (1.8)	1.0
AUC(0-t)*	551.8 (21.0)	594.6 (21.9)	545.0 (20.9)	0.93
LnAUC(0-t)*, Antilog	6.16 (0.04) 474.2	6.20 (0.04) 490.8	6.08 (0.04) 435.2	0.93
AUC(0-inf)*	638.3 (24.8)	684.1 (25.9)	637.0 (24.6)	0.93
LnAUC(0-inf)*, Antilog	6.31 (0.03) 549.2	6.33 (0.03) 562.2	6.25 (0.03) 518.9	0.98
Cmax*	101.9 (17.5)	123.4 (18.3)	173.5 (17.4)	0.83
LnCmax*, Antilog	4.58 (0.11) 97.2	4.70 (0.11) 109.6	4.93 (0.10) 138.8	0.89

* = LSMEANS

L. ADVERSE EFFECTS : The firm has documented adverse effects for all 18 subjects starting the study. The adverse events included were headache, decrease in the diastolic blood pressure, tachycardia, tingling scalp, lightheadedness, chest pain, stomach cramp,

diarrhea, sore throat etc. The side effects were of mild severity with possible to probable relationship with the drug. The events occurred with similar frequency across the three treatments. Subject #9 was transported to the hospital for evaluation. It was found to be non-study drug related chest pain. The adverse events are listed in Attachment 2.

M. COMMENTS FOR THE POST PRANDIAL BIO-STUDY :

1. From Table BST 2.1, one could see that the test (fed) and reference (fed) formulation mean plasma levels and standard deviations are similar after 2 hr sample point.

2. Table BST 2.2 indicates that the test mean pharmacokinetic parameters are within 20% of the reference. Compared with the test (fed) treatment, the test (fasting) treatment Cmax's were significantly higher and occurred early indicating that food may reduce the rate of drug absorption. The area under the curve parameter was similar with or without food challenge, indicating that food may not alter labetalol extent of absorption. The half-lives are similar for all the three treatments. The mean AUC(0-t) parameter was more than 86% of the mean AUC(0-inf) parameter implying adequate sampling duration.

VI.DISSOLUTION METHODOLOGY : The firm has used the following USP XXIII recommended dissolution testing methodology and specifications for the comparative dissolutions of the test and reference formulations.

Apparatus: USP XXIII, 2 (paddle)
Speed: 50 rpm
Medium: Deaerated Water
Volume: 900 ml

A. RESULTS OF THE DISSOLUTION TESTING : The comparative dissolutions for the 100 mg, 200 mg and 300 mg test and reference tablet formulations are given in Table D.

B. COMMENTS ABOUT THE DISSOLUTION TESTING :

1. Table 'D' indicates that the reference formulation dissolution for all the three strengths has a higher %CV at 10 minutes sample point than that of the test formulation. Compared to the test, the mean reference dissolution at 10 minute sample point is also relatively low implying a relatively slow initial dissolution rate.

2. Both the test and reference formulations pass the USP recommended 'Q' comfortably.

VII.OVERALL COMMENTS :

1. The firm has reported adverse effects for all study subjects in both studies. The adverse events, though of mild severity, were possibly or probably related to the drug treatments. In the fasting study, out of 40 participating subjects, 3 dropped out i.e. the total drop-outs constituted 7.5%. It is however noted that none of these drop-outs were study drug (labetalol) related. In the "food challenge" study, out of 18 participating subjects, 5 dropped out i.e. the total drop-out percentage was 38. None of the 5 drop-outs however, was study drug (labetalol) related. (One subject drop-out #9, was thought to be study-drug related. In the hospital however, the chest pain was found to be non-cardiac.)

2. Also, after looking at the plasma level data it could be stated that the linear range of 5-200 ng/ml was not wide enough, considering more than 200 ng/ml concentrations, seen in many subjects such as 5, 13, 15, 26, 30 for the fasting study and subjects 1, 5, 11, 13 (zenith, fasting treatment) in the "food challenge" study. To overcome this problem, the firm has used dilutions to bring the concentrations within the linearity range. A total of 9 samples were reassayed this way. The results and the dilution factors are listed in Attachment 3.

3. It is interesting that none of the 200 mg and 300 mg strength test formulation individual unit dissolutions reached 100% release in 60 minutes sample duration. The 100 mg reference formulation mean dissolution was considerably slower at 10 minute sample point compared to the test formulation.

VIII.RECOMMENDATIONS :

1. The bioequivalence study conducted by Zenith-Goldline Labs on its 200 mg labetalol hydrochloride tablet, lot # ND-241, comparing it to Schering's Normodyne^{R} 200 mg tablet, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Zenith-Goldline Labs, labetalol hydrochloride 200 mg tablet is bioequivalent to the reference product Normodyne^{R} 200 mg tablet manufactured by Schering Labs.

2. The dissolution testing data conducted by Zenith-Goldline Labs on its Labetalol hydrochloride 100 mg tablet, 200 mg tablet, and 300 mg tablet, lot #ND-242, ND-241, and ND-243 respectively are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of

deaerated water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of the drug in the dosage form is dissolved in minutes.

Note : The reviewer is not convinced that a fasting bio-equivalency study cannot be conducted on the 300 mg tablet test formulation using normal subjects, for the following reasons:

I. The information in the research articles, (provided with the application), indicates that bio-studies have been conducted in the past, using labetalol dose greater than 300 mg.

II. The drug has a high first-pass, the extraction ratio being 80%-90%, leading to low levels of drug in plasma relative to dose.

III. The "food challenge" may raise some safety concerns due to literature reported higher bioavailability. However, since only one subject dropped out of the currently conducted 'food challenge' study (due to non study-drug related chest pain), the argument does not appear to be totally convincing for the waiver of the 300 mg strength tablet formulation.

IV. It is debatable whether the reported 'adverse' events may be categorized as 'expected' or 'adverse'.

Based on the above points I-IV, the following determinations are made.

4. The formulations for 100 mg and 300 mg strengths are proportionally similar to the 200 mg strength of the test product which underwent bioequivalency testing. The waiver of in-vivo bioequivalency study requirements for the 100 mg test product is granted. The 100 mg test product is therefore deemed bioequivalent to the 100 mg tablet of Normodyne® manufactured by Schering Labs.

5. The firm has not conducted an acceptable in-vivo bioequivalency study on the 300 mg strength labetalol hydrochloride tablet formulation. The waiver of in-vivo testing may not be granted for the 300 mg formulation. The firm should conduct an acceptable in-vivo bioequivalency study/ies on this drug product strength.

7S/

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG See NOTE on page 21 of this review
Concur: 8/10/06 Date:_____

Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-787 (Original, Duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Sathe), Drug File, Division File.

Table D . In Vitro Dissolution Testing

Drug (Generic Name): Labetalol Hydrochloride
Dose Strength: 100 mg, 200 mg and 300 mg tablet
ANDA No.: 74-787
Firm: Zenith-Goldline Labs.
Submission Date: November 14, 1995
File Name: 74787SDW.N95

I. Conditions for Dissolution Testing:

USP XXIII Method 2, Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water, Volume: 900 ml
Specifications: NLT % (Q) dissolved in minutes
Reference Drug: Normodyne^{R} Tablet
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product : Zenith's Labetalol HCl Tablet Lot # ND-242 Strength (100 mg)			Reference Product : Normodyne^{R} Tablet Lot # 01294 Strength (100 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	93.8		3.4	59.9		32.4
20	95.8		2.4	100.9		1.2
30	96.4		2.2	101.3		1.4
45	96.7		2.3	101.4		1.4
60	96.9		2.3	101.6		1.2

Sampling Times (Minutes)	Test Product : Zenith's Labetalol HCl tablet Lot # ND-241 Strength (200 mg)			Reference Product : Normodyne[R] tablet Lot # 94063 Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	90.9		4.7	89.4		16.8
20	92.7		3.3	97.7		7.1
30	93.7		2.7	98.9		3.2
45	94.1		2.1	99.7		1.1
60	94.3		2.0	100.1		0.7

Sampling Times (Minutes)	Test Product : Zenith's Labetalol HCl tablet Lot # ND-243 Strength (300 mg)			Reference Product : Normodyne[R] tablet Lot # 94998 Strength (300 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	91.6		3.2	81.7		16.6
20	94.5		1.5	99.8		1.4
30	95.0		1.5	100.5		0.6
45	95.3		1.3	100.5		0.6
60	95.4		1.2	100.4		0.7

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
1	10/01/94	0930	Itchy, tingling scalp	Mild	1400	None	None	Schering
	10/01/94	0943	Headache	Mild	1400	Possible	None	Schering
	10/08/94	0830	Itchy, tingling scalp	Mild	1100	None	None	Zenith
	10/08/94	0835	Chills	Mild	1000	None	None	Zenith
	10/08/94	0900	Occipital headache	Mild	1010	Possible	None	Zenith
2	10/08/94	0925	Frontal headache	Mild	1200	Possible	None	Schering
3	10/01/94	0949	Sleepy	Mild	1350	Possible	None	Zenith
	10/01/94	1022	Decreased diastolic bp	Mild	1055	Probable	*	Zenith
	10/01/94	1235	Decreased diastolic bp	Mild	1243	Probable	Monitor	Zenith
	10/08/94	1136	Decreased diastolic bp	Mild	1142	Probable	Monitor	Schering
4	10/01/94	0950	Tired, headache	Mild	10/02/94 1800	Possible	None	Schering
	10/01/94	Not reported	Right forearm ecchymoses	Mild	Unresolved at discharge	None	None	Schering
	10/08/94	1236	Decreased diastolic bp	Mild	1241	Probable	Monitor	Zenith

* - Monitor, electrocardiogram.

Attachment 1

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
5	** 09/29/94	0900	Headache	Mild	10/02/94 0730	None	None	Schering
	10/01/94	0904	Decreased diastolic bp	Mild	0909	Probable	Monitor	Schering
	10/01/94	0907	Increased standing bp	Mild	0915	None	Monitor	Schering
	10/01/94	0810	Itchy, tingling scalp	Mild	2000	None	None	Schering
	10/08/94	0823	Itching scalp	Mild	2000	None	None	Zenith
	10/08/94	1150	Tachycardia - standing	Mild	1158	Possible	None	Zenith
	10/08/94	1239	Decreased standing bp	Mild	1244	Probable	Monitor	Zenith
	10/08/94	1630	Headache - posterior occipital, neck	Mild	0700	Possible	Rest	Zenith
6	10/01/94	0954	Tired	Mild	1800	Possible	None	Zenith
	10/01/94	1345	Tachycardia - standing	Mild	1350	Possible	Monitor	Zenith
	10/01/94	1330	Headache	Mild	10/02/94 1800	Possible	None	Zenith
	10/08/94	0925	Frontal headache	Mild	2000	Possible	None	Schering
7	10/01/94	0957	Decreased diastolic bp	Mild	1004	Probable	Monitor	Schering
	10/01/94	1141	Decreased diastolic bp	Mild	1147	Probable	Monitor	Schering
	10/01/94	1240	Decreased diastolic bp	Mild	1248	Probable	Monitor	Schering
	10/01/94	1250	Decreased diastolic bp standing.	Mild	1315	Probable	Monitor	Schering

* - Monitor, electrocardiogram.
** - Reported at entry of phase II, 10/07/94.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
7	** 10/06/94	Not reported	Sinus congestion	Mild	10/07/94 Morning	None	Self admin. Robitussin® cough drop	Schering
	10/08/94	0840	Decreased diastolic bp	Mild	0900	Probable	*	Zenith
	10/08/94	1000	Decreased diastolic bp	Mild	1011	Probable	*	Zenith
	10/08/94	1058	Decreased diastolic bp	Mild	1147	Probable	*	Zenith
	10/08/94	1200	Congested, stuffy nose	Mild	2000	None	None	Zenith
	10/08/94	1246	Decreased diastolic bp	Mild	1302	Probable	*	Zenith
	10/08/94	1310	Decreased diastolic bp	Mild	1329	Probable	*	Zenith
	10/08/94	1403	Decreased diastolic bp	Mild	1421	Probable	*	Zenith
8	10/08/94	0916	Decreased standing bp	Mild	0929	Probable	Monitor	Schering
	10/08/94	1247	Decreased diastolic bp	Mild	1252	Probable	Monitor	Schering
9	10/01/94	0920	Lightheaded, nausea, blurred vision following standing for blood pressure measurement.	Mild	0926	Possible	Supine position	Zenith
	10/01/94	1033	Decreased diastolic bp	Mild	1038	Probable	Monitor	Zenith
	10/01/94	1354	Tachycardia - standing	Mild	1405	Possible	Monitor	Zenith
	10/08/94	0920	Decreased diastolic bp	Mild	0932	Probable	Monitor	Schering
	10/08/94	0924	Decreased diastolic bp standing	Mild	0929	Probable	Monitor	Schering

* - Monitor, electrocardiogram.
** - Reported at entry of phase II, 10/07/94.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
9	10/08/94	0943	Decreased diastolic bp standing	Mild	0955	Probable	Monitor	Schering
	10/08/94	0949	Nausea	Mild	0952	Possible	None	Schering
	10/08/94	1130	Tired	Mild	2200	Possible	None	Schering
	10/08/94	1323	Decreased diastolic bp standing	Mild	1328	Probable	Monitor	Schering
	10/08/94	1405	Decreased diastolic bp	Mild	1411	Probable	Monitor	Schering
	10/08/94	1413	Decreased diastolic bp standing	Mild	1419	Probable	Monitor	Schering
10	10/01/94	0928	Decreased diastolic bp	Mild	0933	Probable	Monitor	Schering
	10/01/94	1700	Frontal headache	Mild	10/02/94 0200	Possible	None	Schering
	10/08/94	0850	Runny nose	Mild	Not reported	None	None	Zenith
	10/08/94	0922	Decreased diastolic bp	Mild	0930	Probable	Monitor	Zenith
	10/08/94	0946	Decreased diastolic bp	Mild	10/09/94 1007	Probable	*	Zenith
	10/08/94	0945	Pressure to the head	Mild	1046	Possible	None	Zenith
	10/08/94	1257	Decreased diastolic bp	Mild	1305	Probable	Monitor	Zenith
	10/08/94	1320	Decreased diastolic bp	Mild	1325	Probable	Monitor	Zenith
	10/08/94	1800	Generalized headache	Mild	0700	Possible	Rest	Zenith
	10/08/94	2145	Nausea	Mild	0700	Possible	Rest	Zenith

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
11	10/01/94	1252	Decreased diastolic bp	Mild	1310	Possible	*	Zenith
	10/08/94	1222	Decreased bp	Mild	1228	Possible	Monitor	Schering
	10/08/94	1300	Tachycardia - standing	Mild	1306	Possible	Monitor	Schering
			Tachycardia - standing	Mild	1330	Possible	Monitor	Schering
12	10/01/94	1255	Decreased diastolic bp	Mild	1303	Probable	Monitor	Schering
13	10/01/94	1156	Decreased diastolic bp	Mild	1202	Probable	Monitor	Schering
	10/08/94	0915	Nausea	Mild	1330	Possible	None	Zenith
	10/08/94	0915	Lightheaded	Mild	1330	Possible	None	Zenith
	10/08/94	1030	Occipital headache	Mild	2000	Possible	Ice pack	Zenith
14	10/01/94	1159	Decreased diastolic bp	Mild	1211	Probable	None	Zenith
	10/01/94	1302	Tachycardia - standing	Mild	1334	Possible	Monitor	Zenith
	** 10/04/94	Evening	Generalized headache	Mild	Evening	Possible	Self admin. 2 tabs. Tylenol®	Zenith
	10/08/94	1055	Tachycardia - standing	Mild	1112	Possible	Monitor	Schering
	10/08/94	1121	Tachycardia - standing	Mild	1207	Possible	Monitor	Schering
	10/08/94	1232	Tachycardia - standing	Mild	1247	Possible	Monitor	Schering
	10/08/94	1311	Tachycardia - standing	Mild	1345	Possible	Monitor	Schering
	10/08/94	1338	Tachycardia - standing	Mild	1345	Possible	Monitor	Schering
	10/08/94	1416	Tachycardia - standing	Mild	1425	Possible	Monitor	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
15	10/01/94	0930	Itchy, tingling scalp	Mild	10/02/94 1500	None	None	Schering
	10/01/94	1052	Decreased bp	Mild	1110	Probable	*	Schering
16	10/01/94	1201	Decreased diastolic bp	Mild	1206	Probable	*	Zenith
	10/08/94	1055	Decreased standing bp	Mild	1100	Probable	Monitor	Schering
	10/08/94	1126	Decreased standing bp	Mild	1158	Probable	Monitor	Schering
	10/08/94	1201	Decreased diastolic bp	Mild	1249	Probable	*	Schering
17	10/01/94	1106	Lightheaded after standing for blood pressure measurement	Mild	1107	Possible	Seated	Schering
18	10/01/94	1320	Headache	Mild	Unknown	Possible	None	Zenith
	10/01/94	1730	Occipital headache	Moderate	10/02/94 2230	Possible	Ice pack	Zenith
	10/08/94	0959	Decreased standing bp	Mild	1004	Probable	Monitor	Schering
	10/08/94	1000	Headache	Mild	2000	Possible	None	Schering
	10/08/94	1000	Lightheaded/dizzy	Mild	2000	Possible	None	Schering
	10/08/94	1102	Decreased diastolic bp	Mild	1108	Probable	Monitor	Schering
	10/08/94	1132	Decreased standing bp	Mild	1140	Probable	Monitor	Schering
	10/08/94	1205	Decreased diastolic bp	Mild	1224	Probable	*	Schering
	10/08/94	1246	Decreased standing bp	Mild	1251	Probable	Monitor	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
19	10/01/94	0944	Decreased diastolic bp	Mild	0949	Probable	Monitor	Zenith
	10/01/94	1210	Decreased diastolic bp	Mild	1216	Probable	Monitor	Zenith
	10/01/94	1428	Decreased diastolic bp	Mild	1433	Probable	Monitor	Zenith
	10/08/94	0911	Decreased diastolic bp	Mild	0915	Probable	Monitor	Schering
	10/08/94	1104	Decreased diastolic bp	Mild	1124	Probable	*	Schering
	10/08/94	1352	Decreased diastolic bp	Mild	1357	Probable	Monitor	Schering
20	10/01/94	1211	Increased standing bp	Mild	1226	None	Monitor	Schering
21	10/09/94	1231	Decreased diastolic bp	Mild	1236	Probable	Monitor	Schering
	10/16/94	0921	Decreased diastolic bp	Mild	0941	Probable	*	Zenith
	10/16/94	1045	Decreased diastolic bp	Mild	1050	Probable	Monitor	Zenith
	10/16/94	1153	Bradycardia	Mild	1158	Probable	Monitor	Zenith
	10/16/94	1300	Bradycardia	Mild	1308	Probable	Monitor	Zenith
22	10/09/94	0922	Increased standing bp	Mild	0927	None	Monitor	Zenith
	10/10/94	0100	Throbbing headache	Moderate	0600	Possible	Ice pack	Zenith
23	10/16/94	0904	Lightheaded - standing	Mild	0906	None	None	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
24	10/09/94	0950	Tired	Mild	1300	Possible	None	Schering
	10/09/94	1131	Decreased diastolic bp	Mild	1136	Probable	Monitor	Schering
	10/09/94	1236	Decreased diastolic bp	Mild	1241	Probable	Monitor	Schering
	10/09/94	1400	Decreased diastolic bp	Mild	1411	Probable	Monitor	Schering
	10/16/94	0824	Decreased diastolic bp	Mild	0829	Probable	Monitor	Zenith
25	10/09/94	0929	Lightheaded	Mild	1025	Possible	Supine position	Schering
	10/09/94	0929	Nausea	Mild	1025	Possible	Supine position	Schering
	10/09/94	1058	Nausea	Mild	1135	Possible	Supine position	Schering
26	10/09/94	1307	Decreased diastolic bp	Mild	1313	Probable	Monitor	Zenith
	10/16/94	0929	Decreased diastolic bp	Mild	0934	Probable	Monitor	Schering
	10/16/94	1309	Decreased diastolic bp	Mild	1330	Probable	Monitor	Schering
27	10/09/94	1246	Decreased diastolic bp	Mild	1255	Probable	Monitor	Zenith
	10/09/94	1404	Decreased diastolic bp	Mild	1408	Probable	Monitor	Zenith
	10/09/94	2130	Headache	Mild	2210	Possible	None	Zenith
	10/16/94	1141	Decreased diastolic bp	Mild	1146	Probable	Monitor	Schering
	10/16/94	1312	Decreased standing bp	Mild	1318	Probable	Monitor	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
29	10/09/94	0937	Lightheaded	Mild	0940	Possible	None	Zenith
	10/09/94	1253	Decreased standing bp, tachycardia	Mild	1259	Probable	Monitor	Zenith
	10/09/94	1316	Decreased diastolic bp	Mild	1329	Probable	Monitor	Zenith
	10/16/94	1032	Decreased diastolic bp	Mild	1038	Probable	*	Schering
	10/16/94	1040	Decreased bp	Mild	1045	Probable	Monitor	Schering
	10/16/94	1313	Decreased diastolic bp	Mild	1335	Probable	*	Schering
	10/16/94	1337	Tachycardia - standing	Mild	1342	Probable	Monitor	Schering
30	10/16/94	1038	Decreased standing bp	Mild	1043	Probable	Monitor	Zenith
31	10/09/94	1034	Decreased bp, lightheaded	Mild	1050	Probable	Monitor	Zenith
	10/09/94	1140	Decreased diastolic bp	Mild	1145	Probable	Monitor	Zenith
	10/09/94	1148	Decreased standing bp, lightheaded	Mild	1255	Probable	Supine	Zenith
	10/09/94	1352	Decreased diastolic bp, tachycardia	Mild	1402	Probable	Monitor	Zenith
	10/09/94	1300	Frontal headache	Mild	1700	Possible	None	Zenith
	10/09/94	1435	Nausea	Mild	1700	Possible	None	Zenith
	10/16/94	1145	Decreased diastolic bp	Mild	1152	Probable	Monitor	Schering
	10/16/94	1200	Frontal headache	Mild	2350	Possible	Rest	Schering
	10/16/94	1324	Decreased standing bp	Mild	1329	Probable	Monitor	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
32	10/09/94	0901	Decreased diastolic bp	Mild	0909	Probable	Monitor	Schering
	10/09/94	1303	Decreased diastolic bp	Mild	1324	Probable	Monitor	Schering
	10/16/94	0946	Decreased standing bp	Mild	0951	Probable	Monitor	Zenith
	10/16/94	1218	Tachycardia - standing	Mild	1222	Probable	Monitor	Zenith
	10/16/94	1600	Generalized headache	Mild	10/17/94 0200	Possible	Rest	Zenith
34	10/09/94	0903	Decreased diastolic bp	Mild	0908	Probable	Monitor	Zenith
	10/09/94	1010	Tachycardia - standing	Mild	1015	Probable	Monitor	Zenith
	10/09/94	1112	Decreased diastolic bp	Mild	1117	Probable	Monitor	Zenith
	10/09/94	1119	Decreased diastolic bp tachycardia - standing	Mild	1128	Probable	Monitor	Zenith
	10/09/94	1148	Standing tachycardia	Mild	1152	Probable	Monitor	Zenith
	10/09/94	1217	Standing tachycardia	Mild	1222	Probable	Monitor	Zenith
	10/09/94	1306	Decreased diastolic bp	Mild	1319	Probable	Monitor	Zenith
	10/09/94	1321	Decreased diastolic bp tachycardia	Mild	1335	Probable	Monitor	Zenith
	10/09/94	1420	Decreased standing bp	Mild	1426	Probable	Monitor	Zenith
	10/16/94	0846	Decreased diastolic bp standing	Mild	0852	Probable	Monitor	Schering
	10/16/94	0944	Decreased diastolic bp	Mild	1018	Probable	*	Schering
	10/16/94	1159	Decreased diastolic bp	Mild	1205	Probable	Monitor	Schering
	10/16/94	1220	Decreased diastolic bp	Mild	1225	Probable	Monitor	Schering
	10/16/94	1328	Decreased diastolic bp	Mild	1403	Probable	*	Schering
	10/16/94	1600	Generalized headache	Mild	1700	Possible	Rest	Schering

* - Monitor, electrocardiogram.

TABLE 5: ADVERSE EVENTS
LABETALOL TABLETS
#037-67-10756

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	TREATMENT	PRODUCT UNDER STUDY
35	10/09/94	1004	Decreased diastolic bp	Mild	1009	Probable	Monitor	Zenith
36	10/09/94	1332	Decreased diastolic bp	Mild	1339	Probable	Monitor	Schering
	10/16/94	0954	Decreased diastolic bp	Mild	0959	Probable	Monitor	Zenith
	10/16/94	1222	Decreased diastolic bp	Mild	1227	Probable	Monitor	Zenith
37	10/16/94	0956	Decreased diastolic bp	Mild	1002	Probable	Monitor	Schering
	10/16/94	1229	Decreased diastolic bp	Mild	1234	Probable	Monitor	Schering
	10/16/94	1404	Decreased diastolic bp	Mild	1412	Probable	Monitor	Schering
40	10/09/94	1321	Decreased diastolic bp	Mild	1326	Probable	Monitor	Zenith
	10/16/94	1030	Decreased diastolic bp	Mild	1035	Probable	Monitor	Schering

* - Monitor, electrocardiogram.

Figure 1: Mean Labetalol Plasma Levels

n = 13

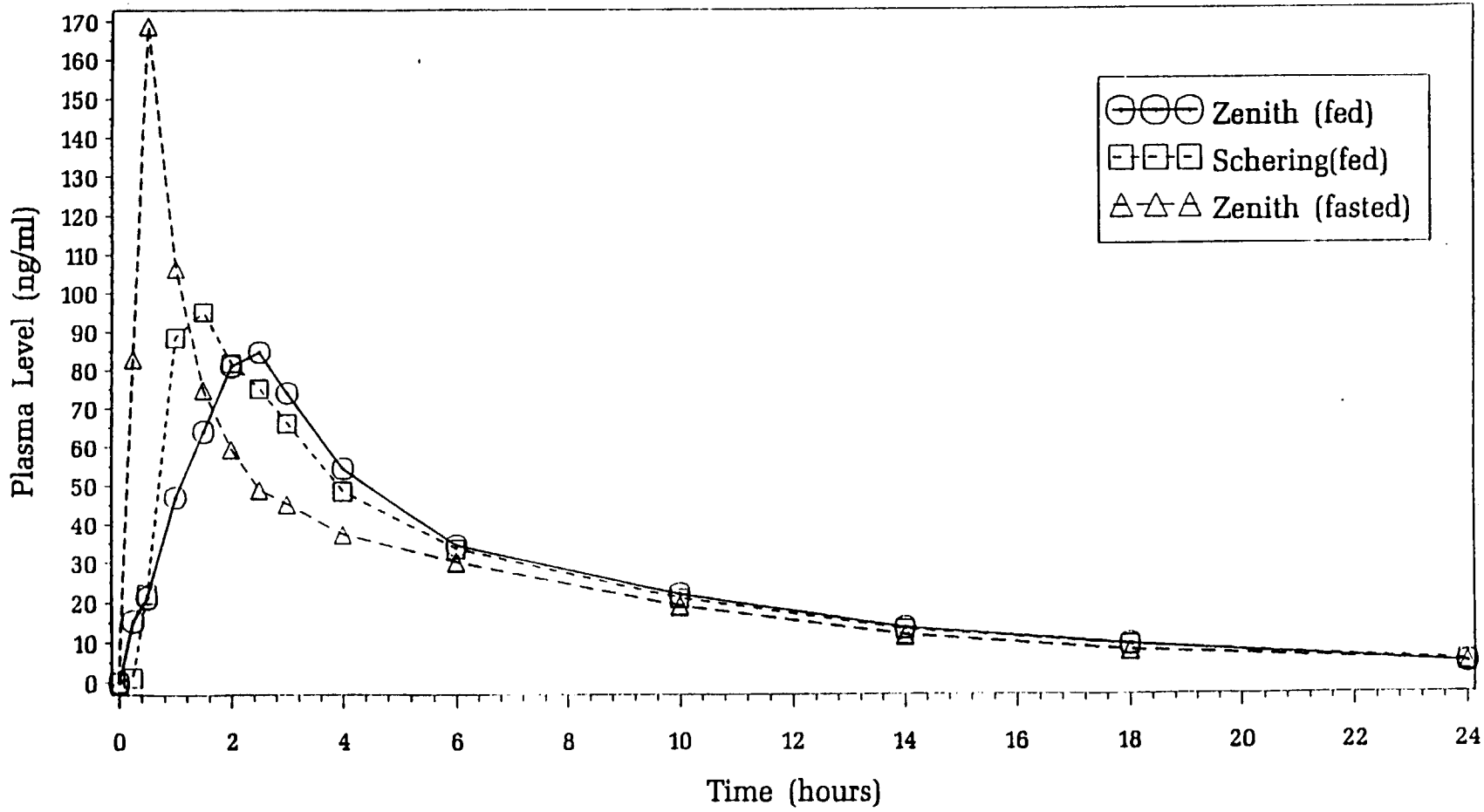


TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
1	01/26/95	1112	Headache	Mild	01/26/95 1515	Possible	None	Zenith(fed)
	02/02/95	1432	Decreased standing diastolic BP	Mild	02/02/95 1437	Probable	Monitor	Zenith(fasted)
	02/09/95	1116	Decreased standing diastolic BP	Mild	02/09/95 1123	Probable	Monitor	Schering(fed)
	02/09/95	1234	Decreased standing diastolic BP	Mild	02/09/95 1239	Probable	Monitor	Schering(fed)
	02/09/95	1258	Decreased standing diastolic BP	Mild	02/09/95 1314	Probable	Monitor	Schering(fed)
	02/09/95	1332	Decreased standing diastolic BP	Mild	02/09/95 1348	Probable	Monitor	Schering(fed)
	02/09/95	1432	Decreased standing diastolic BP	Mild	02/09/95 1437	Probable	Monitor	Schering(fed)
2	02/06/95	0200	Stomach cramps	Mild	02/06/95 0300	None	Self-admin. Kaopectate 2 tbsp.	Zenith(fasted)
3	01/26/95	1352	Tachycardia	Mild	01/26/95 1409	Possible	None	Zenith(fasted)
	02/02/95	1040	Scalp tingling and numbness	Mild	02/02/95 2030	None	None	Zenith(fed)
	02/02/95	1153	Decreased standing BP	Mild	02/02/95 1207	Probable	Monitor	Zenith(fed)
	02/02/95	1257	Tachycardia	Mild	02/02/95 1305	Possible	Monitor	Zenith(fed)
	02/09/95	1025	Tingling scalp	Mild	02/09/95 1900	None	None	Schering(fed)
	02/09/95	1434	Decreased supine diastolic BP	Mild	02/09/95 1439	Probable	Monitor	Schering(fed)

Attachment 2
3 16

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
4	01/26/95	0927	Tachycardia	Mild	01/26/95 0928	Possible	Monitor	Zenith(fed)
	01/26/95	0955	Tachycardia	Mild	01/26/95 1002	Possible	Monitor	Zenith(fed)
	01/26/95	1040	Decreased supine BP	Mild	01/26/95 1058	Probable	Monitor	Zenith(fed)
	01/26/95	1145	Decreased supine BP	Mild	01/26/95 1149	Probable	Monitor	Zenith(fed)
	01/26/95	1235	Left inner thigh muscle spasm	Mild	01/26/95 1236	None	None	Zenith(fed)
	01/26/95	1245	Decreased supine BP	Mild	01/26/95 1351	Probable	Monitor	Zenith(fed)
5	01/26/95	0958	Decreased diastolic BP	Mild	01/26/95 1049	Probable	Monitor	Zenith(fasted)
	01/26/95	1212	Decreased diastolic BP	Mild	01/26/95 1220	Probable	Monitor	Zenith(fasted)
	01/26/95	1358	Tachycardia	Mild	01/26/95 1511	Possible	None	Zenith(fasted)
	01/26/95	1411	Decreased diastolic BP	Mild	01/26/95 1420	Probable	Monitor	Zenith(fasted)
	02/02/95	1011	Standing tachycardia	Mild	02/02/95 1018	Possible	Monitor	Schering(fed)
	02/02/95	1031	Decreased diastolic BP	Mild	02/02/95 1050	Probable	Monitor	Schering(fed)
	02/02/95	1031	Standing tachycardia	Mild	02/20/95 1050	Possible	Monitor	Schering(fed)
	02/02/95	1127	Decreased diastolic BP	Mild	02/02/95 1201	Probable	Monitor	Schering(fed)
	02/02/95	1127	Standing tachycardia	Mild	02/02/95 1201	Possible	Monitor	Schering(fed)
	02/02/95	0959	Standing tachycardia	Mild	02/02/95 1050	Possible	Monitor	Schering(fed)
	02/02/95	1156	Lightheaded	Mild	02/02/95 1157	Possible	None	Schering(fed)
	02/02/95	1237	Decreased diastolic BP	Mild	02/02/95 1242	Probable	Monitor	Schering(fed)
	02/02/95	1237	Standing tachycardia	Mild	02/02/95 1242	Possible	Monitor	Schering(fed)
	02/02/95	1258	Decreased supine diastolic BP	Mild	02/02/95 1304	Probable	Monitor	Schering(fed)
	02/02/95	1337	Decreased supine BP	Mild	02/02/95 1342	Probable	Monitor	Schering(fed)

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
5	02/02/95	1343	Decreased standing BP	Mild	02/02/95 1348	Probable	Monitor	Schering(fed)
	02/02/95	1343	Standing tachycardia	Mild	02/02/95 1348	Possible	Monitor	Schering(fed)
	02/02/95	1418	Standing tachycardia	Mild	02/02/95 1424	Possible	Monitor	Schering(fed)
	02/02/95	1507	Decreased seated diastolic BP	Mild	02/02/95 1704	Probable	Monitor	Schering(fed)
	02/09/95	1121	Lightheaded	Mild	02/09/95 1122	Possible	None	Zenith(fed)
	02/09/95	1027	Standing tachycardia	Mild	02/09/95 1032	Possible	Monitor	Zenith(fed)
	02/09/95	1054	Standing tachycardia	Mild	02/09/95 1100	Possible	Monitor	Zenith(fed)
	02/09/95	1121	Decreased standing BP	Mild	02/02/95 1128	Probable	Monitor	Zenith(fed)
	02/09/95	1121	Standing tachycardia	Mild	02/09/95 1128	Possible	Monitor	Zenith(fed)
	02/09/95	1150	Standing tachycardia	Mild	02/09/95 1201	Possible	Monitor	Zenith(fed)
	02/09/95	1240	Standing tachycardia	Mild	02/09/95 1316	Possible	Monitor	Zenith(fed)
	02/09/95	1304	Decreased standing diastolic BP	Mild	02/09/95 1316	Probable	Monitor	Zenith(fed)
	02/09/95	1304	Standing tachycardia	Mild	02/09/95 1316	Possible	Monitor	Zenith(fed)
	02/09/95	1337	Decreased standing diastolic BP	Mild	02/09/95 1416	Probable	Monitor	Zenith(fed)
	02/09/95	1337	Standing tachycardia	Mild	02/09/95 1416	Possible	Monitor	Zenith(fed)
	02/09/95	1405	Decreased supine diastolic BP	Mild	02/09/95 1414	Probable	Monitor	Zenith(fed)
	02/09/95	1435	Decreased supine diastolic BP	Mild	02/09/95 1440	Probable	Monitor	Zenith(fed)

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
6	01/26/95	1258	Decreased diastolic BP	Mild	01/26/95 1301	Probable	None	Schering(fed)
	01/26/95	1303	Tachycardia	Mild	01/26/95 1316	Possible	None	Schering(fed)
	01/26/95	1313	Decreased diastolic BP	Mild	01/26/95 1315	Probable	Monitor	Schering(fed)
	01/26/95	1355	Decreased diastolic BP	Mild	01/26/95 1359	Probable	Monitor	Schering(fed)
	01/26/95	1412	Decreased supine diastolic BP	Mild	01/26/95 1425	Probable	Monitor	Schering(fed)
	02/02/95	1126	Decreased diastolic BP	Mild	02/02/95 1131	Probable	Monitor	Zenith(fed)
	02/02/95	1132	Decreased systolic BP	Mild	02/02/95 1137	Probable	Monitor	Zenith(fed)
	02/02/95	1300	Decreased supine diastolic BP	Mild	02/02/95 1321	Probable	Monitor	Zenith(fed)
	02/02/95	1420	Standing tachycardia	Mild	02/02/95 1426	Possible	Monitor	Zenith(fed)
	02/09/95	1033	Decreased standing BP	Mild	02/09/95 1039	Probable	Monitor	Zenith(fasted)
7	02/02/95	1034	Decreased standing BP	Mild	02/02/95 1103	Probable	Monitor	Zenith(fed)
	02/02/95	1133	Decreased supine BP	Mild	02/02/95 1138	Probable	Monitor	Zenith(fed)
	02/02/95	1138	Decreased standing BP	Mild	02/02/95 1143	Probable	Monitor	Zenith(fed)
	02/02/95	1140	"Hearing sizzling sound"	Mild	02/02/95 1145	None	None	Zenith(fed)
	02/02/95	1420	Headache	Mild	02/02/95 1530	Possible	None	Zenith(fed)
	02/02/95	1204	Decreased standing BP	Mild	02/02/95 1210	Probable	Monitor	Zenith(fed)
	02/02/95	1239	Decreased supine diastolic BP	Mild	02/02/95 1244	Probable	Monitor	Zenith(fed)
	02/02/95	1308	Decreased supine diastolic BP	Mild	02/02/95 1341	Probable	Monitor	Zenith(fed)
	02/02/95	1421	Decreased supine diastolic BP	Mild	02/02/95 1433	Probable	Monitor	Zenith(fed)

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
8	01/26/95	1600	Headache	Mild	01/26/95 2100	Possible	None	Schering(fed)
	01/26/95	1108	Tachycardia	Mild	01/26/95 1308	Possible	Monitor	Schering(fed)
	01/26/95	1320	Tachycardia	Mild	01/26/95 1325	Possible	Monitor	Schering(fed)
	01/26/95	1447	Tachycardia	Mild	01/26/95 1517	Possible	None	Schering(fed)
9	01/26/95	1008	Decreased diastolic BP	Mild	01/26/95 1046	Probable	Monitor	Schering(fed)
	01/26/95	1140	Left sided chest pain	Moderate	01/26/95 1140	Possible	*	Schering(fed)
	01/26/95	1224	Decreased systolic BP	Mild	01/26/95 1545	Probable	Monitor	Schering(fed)
10	01/26/95	1418	Tachycardia	Mild	01/26/95 1422	Possible	Monitor	Zenith(fasted)
	02/02/95	1446	Decreased supine diastolic BP	Mild	02/02/95 1503	Probable	Monitor	Schering(fed)
11	01/26/95	1130	Headache	Mild	01/26/95 1406	Possible	None	Zenith(fasted)
	02/02/95	1519	Left temporal headache	Mild	02/02/95 2000	Possible	None	Zenith(fed)
	02/09/95	1157	Decreased supine diastolic BP	Mild	02/09/95 1250	Probable	Monitor	Schering(fed)
	02/09/95	2200	Sore throat	Mild	02/10/95 0845	None	None	Schering(fed)

* Subject was transported to a local hospital for evaluation. Diagnosed with non-cardiac chest pain. Subject returned to clinic facility and remained under observation until discharge on 01/27/95.

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
12	02/02/95	1353	Decreased supine diastolic BP	Mild	02/02/95 1358	Probable	Monitor	Schering(fed)
	02/09/95	1419	Decreased supine diastolic BP	Mild	02/09/95 1424	Probable	Monitor	Zenith(fasted)
13	01/26/95	0947	Decreased diastolic BP	Mild	01/26/95 0953	Probable	Monitor	Schering(fed)
	01/26/95	1022	Decreased diastolic BP	Mild	01/26/95 1026	Probable	Monitor	Schering(fed)
	01/26/95	1317	Decreased diastolic BP	Mild	01/26/95 1324	Probable	Monitor	Schering(fed)
	01/26/95	1332	Decreased diastolic BP	Mild	01/26/95 1327	Probable	Monitor	Schering(fed)
	02/02/95	1115	Standing tachycardia	Mild	02/02/95 1121	Possible	Monitor	Zenith(fed)
	02/02/95	1331	Decreased standing systolic BP	Mild	02/02/95 1336	Probable	Monitor	Zenith(fed)
	02/09/95	1302	Standing tachycardia	Mild	02/09/95 1307	Possible	Monitor	Zenith(fasted)
	02/09/95	1531	Decreased standing diastolic BP	Mild	02/09/95 1536	Probable	Monitor	Zenith(fasted)
14	02/09/95	1100	Sleepy	Mild	02/09/95 1130	Possible	None	Zenith(fasted)

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
15	01/26/95	1315	Intermittent testicular pain	Mild	01/26/95 1415	None	None	Zenith(fasted)
	01/26/95	1115	Headache	Mild	01/26/95 1530	Possible	None	Zenith(fasted)
	02/02/95	1338	Decreased standing diastolic BP	Mild	02/02/95 1342	Probable	Monitor	Zenith(fed)
	02/09/95	1030	Nauseated	Mild	02/09/95 1600	None	None	Schering(fed)
	02/09/95	1030	Stomach cramp	Mild	02/09/95 1600	None	None	Schering(fed)
16	01/26/95	1035	Tachycardia	Mild	01/26/95 1039	Possible	Monitor	Zenith(fasted)
	01/26/95	1345	Tachycardia	Mild	01/26/95 1347	Possible	Monitor	Zenith(fasted)
	01/26/95	1414	Tachycardia	Mild	01/26/95 1536	Possible	None	Zenith(fasted)
17	01/26/95	1413	Lightheaded	Mild	01/26/95 1414	Possible	None	Schering(fed)
	02/02/95	0953	Increased standing diastolic BP	Mild	02/02/95 1003	None	Monitor	Zenith(fasted)
	02/02/95	1225	Lightheaded	Mild	02/02/95 1900	Possible	None	Zenith(fasted)

TABLE 5: ADVERSE EVENTS
LABETALOL HCL TABLETS
#037-73-10827

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
18	01/26/95	1434	Headache	Mild	01/27/95 0500	Possible	None	Zenith(fed)
	01/26/95	2015	"Bloated feeling"	Mild	01/26/95 2100	Possible	None	Zenith(fed)
	02/02/95	1054	Decreased supine diastolic BP	Mild	02/02/95 1100	Probable	Monitor	Zenith(fasted)
	02/02/95	1700	Headache	Mild	02/02/95 2330	Possible	None	Zenith(fasted)
	02/02/95	2100	Diarrhea	Mild	02/02/95 2330	None	None	Zenith(fasted)
	02/05/95	Morning	Cough	Mild	02/06/95 Morning	None	None	Zenith(fasted)
	02/09/95	1213	Decreased supine diastolic BP	Mild	02/09/95 1255	Probable	Monitor	Schering(fed)

NOTE to ANDA 74-787 (Labetalol Hydrochloride Tablets, 100 mg, 200 mg, and 300 mg)

Sponsor: Zenith Goldline

Submission date: 11/14/95

It is this team leader's opinion that the bio-waiver request for the 300 mg strength should be granted based on the following considerations:

1. The firm's concern on that "the 300 mg dosage strength may produce excessive blood pressure reductions" appeared to be reasonable at the time the study was conducted, even though some of the literature articles have indicated that dosages higher than 300 mg have been used. It is not clear whether these cited studies were all conducted in normotensive subjects. In fact, conducting the BE study on 200 mg did not provide any additional advantage to the firm.

2. The formulation is exactly proportional between the 200 mg and 300 mg strengths.

3. Information in the PDR (page 2278 under pharmacokinetics and metabolism section, 1995 ed.) indicate that "Despite first-pass metabolism there is a linear relationship between oral doses of 100 to 300 mg and peak plasma levels."

4. Acceptable comparative dissolution data (test 200 mg versus test 300 mg, test 300 mg versus reference 300 mg).

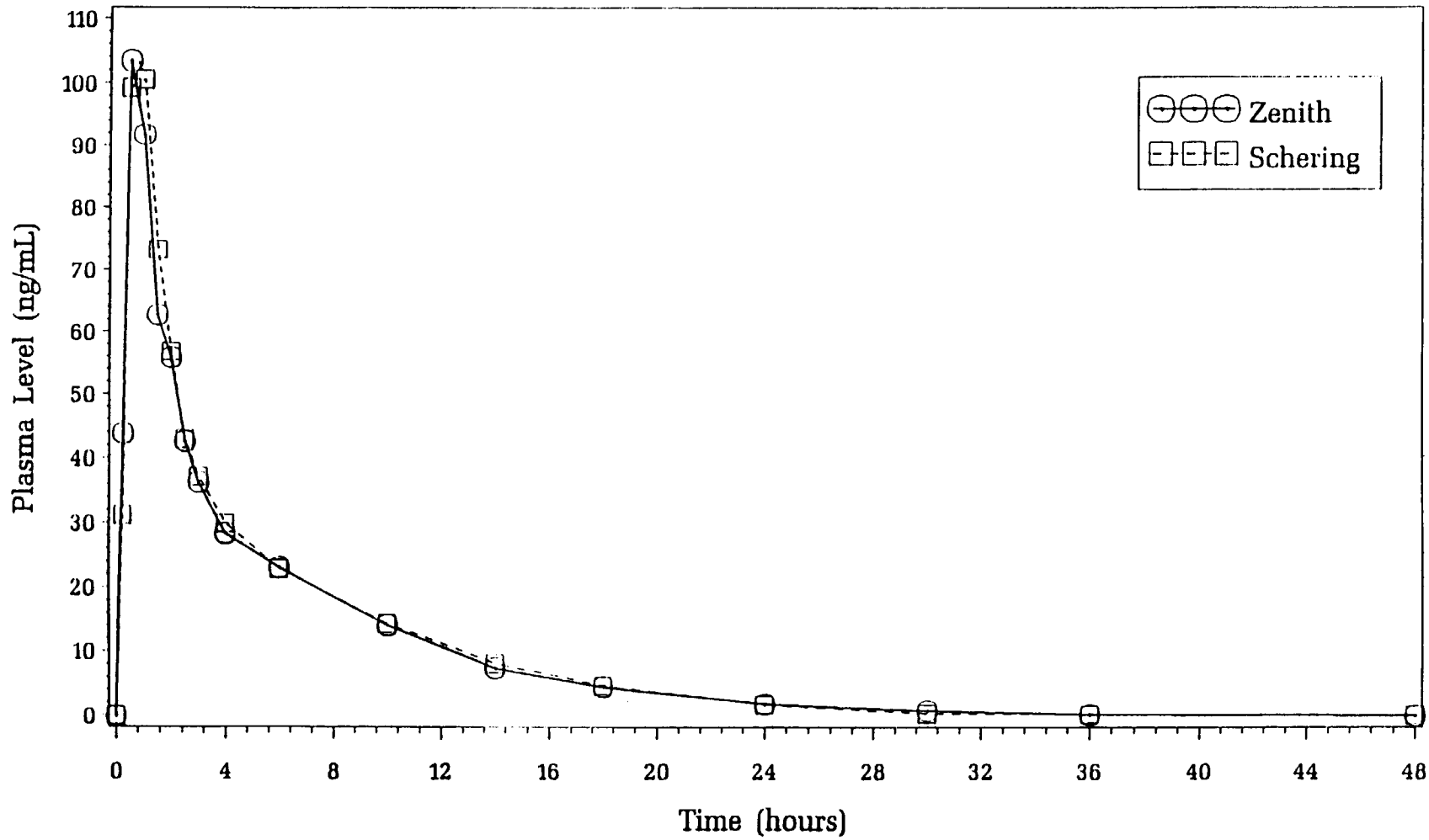
/S/ 6/3/96

Yih-Chain Huang, Ph.D.
Team Leader, Review Branch 1

8/20/96

Figure 1: Mean Labetalol Plasma Levels

n = 37



Attachment B3F 1 of 1